A Framework for Analyzing
Biopharmaceutical Product Introduction in an Emerging Market

by

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B.S. Chemical Engineering, University of California at Berkeley (2001)

Submitted to the Sloan School of Management and the Department of Chemical Engineering
in Partial Fulfillment of the Requirements of

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Abstract

Biopharmaceutical companies are under constant pressure to deliver double-digit growth. In traditional markets such as the U.S., Japan, and the European Union growth is stagnant, and profit margins are falling due to increased price pressure from governments. As a result companies are looking to expand their customer bases. They see such opportunities in the emerging markets of China, India, and Eastern Europe where growth rates are in the double-digits. However, there are risks and uncertainties associated with expansion into emerging markets. These countries lack the regulatory systems and contract-enforcing mechanisms that most companies are used to operating under. In addition, pricing pressure from patients, governments, and healthcare organizations increases attention to the cost of goods.

This document develops a framework for analyzing the potential for introducing a pharmaceutical product into a predetermined emerging market. The framework includes three steps. The first step is market assessment. The second step focuses on the supply chain. Information from market research is used to propose and evaluate alternative operational structures, to reduce costs, and to facilitate market entry. The third step involves financial modeling using Monte Carlo Simulation to account for uncertainty in the information collected from the market assessment and supply chain analysis. The framework is applied in a case study which involves the Genzyme Corporation and evaluates the Chinese market for its cholesterol lowering drug, Cholestagel.

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1 Introduction

1.1 Genzyme Corporation

Genzyme is a biopharmaceutical company with healthcare products for serious diseases. This year marks the 25th anniversary of Genzyme's founding. Since 1981, it has grown from a small start-up into a global leader within the industry, with more than 7,600 employees in 30 countries and product sales in 80 countries. The company's products and services are focused on rare inherited disorders, kidney diseases, orthopedics, cancer, transplantation and immune disease, and diagnostic testing. Figure 1-1 shows major product contribution to Genzyme Corporate 2005 revenue of $2.7 billion (*1*).

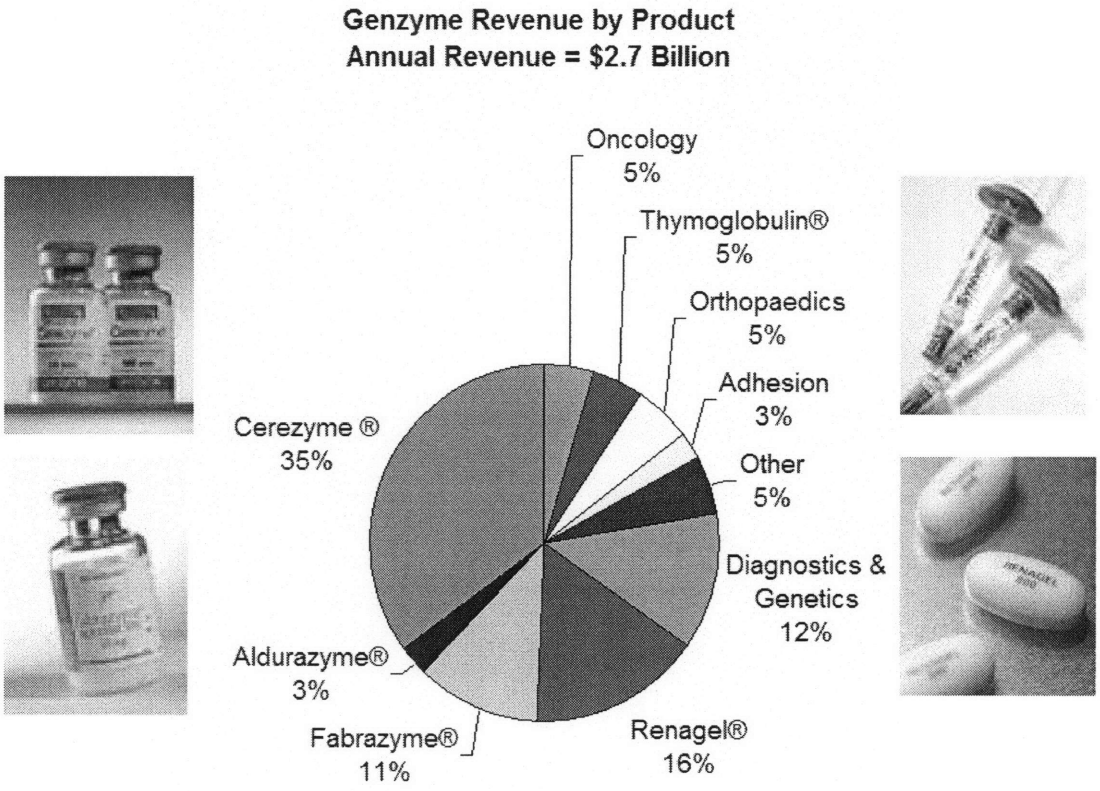


Figure 1-1: Genzyme Product Portfolio-Contribution to Annual Revenue in 2005

Genzyme is arguably best known for its recombinant protein therapeutic product line (Cerezyme, Aldurazyme, and Fabrazyme) for the treatment of lysosomal storage disorders. These three products accounted for nearly 50% of 2005 corporate revenues, which is noteworthy considering that these drugs treat a combined global patient population of approximately 6,500. Genzyme is successful in serving such small patient populations in part because it is actively involved in teaching doctors around the world how to identify these particular disorders. In addition, they commonly work with insurance groups and/or government agencies to get medical treatment for patients. Genzyme's experience in small patient populations along with its vision of meeting

unmet medical needs of communities worldwide has given Genzyme a global outlook for all of its products. As part of the Genzyme vision, the company will exhaustively comb the entire globe to find opportunities for their existing products.

Genzyme actively pursues opportunities to bring in new technology in medical areas where they have a presence and expertise, and in emerging areas where they would like to build a business. Though Genzyme is widely known for its biologics, it is hoping to expand its presence in the small molecule and polymer drug markets as well.

In 2000, Genzyme acquired GelTex Pharmaceuticals for its polymer technology platform and obtained two patent-protected and marketed products, Renagel and WelChol. Renagel is a polymer product used to treat end-stage renal disease for patients undergoing dialysis. In 2005, it was Genzyme's second largest revenue generator at $418 million. WelChol is a polymer based cholesterol lowering agent currently marketed by Sankyo-Parke Davis. This partnership was inherited with the acquisition of GelTex and is limited to the U.S. market. Genzyme controls the rights to market the cholesterol lowering drug under the brand name Cholestagel outside of the U.S. These products bring Genzyme into the market of drug conditions that affect large populations, and are considered important to the company's future growth.

1.2 Project Motivation and Setting

Since 2000, Genzyme has been experiencing impressive growth rates of on average 29% per year (*2*). This success has occurred in part because of Genzyme's commitment to increase diversification of their product portfolio as well as to broaden their worldwide reach. To create long-term sustainability, Genzyme continues to seek opportunities to expand their customer base for their existing products, and see one such opportunity to increase global sales in the emerging markets of China.

China recorded the highest growth rate in the pharmaceutical sector of any single country, up 28% from $7.4bn in 2003 to $9.5 billion in 2004 (*3*). It is currently the ninth largest pharmaceutical market, but is projected to overtake Germany's position as the fourth largest by 2015. Even so, there are a lot of risks and uncertainties associated with expansion into this market. China has complex regulations and distribution networks, as well as lax enforcement of intellectual property laws. In addition, the purchasing power of patients, governments, and healthcare organizations is low. Such a market is unlikely to yield short-term gains.

Genzyme has no illusions about the time and difficulty involved with building presence in an emerging market such as China. In early 2005, Genzyme started an internal effort, the China Initiative Group, to better understand the pharmaceutical market environment in China and coordinate efforts to bring Genzyme products into China. Two offices were opened in 2005, one in Beijing and another in Shanghai. Numerous trips to China were taken through the latter half of the year to assess manufacturing capabilities and to begin talks with regulatory officials.

Genzyme is considering taking Cholestagel, their cholesterol lowering drug, into the urban Chinese market and created a six-month internship to evaluate this opportunity in the fall of

2005. The framework developed and the analysis that follows come from information gathered through a variety of sources including literature reviews, organization-wide interviews and internal resources, and data gathered from primary market research in China.

1.3 Framework

This document develops a framework for analyzing the potential for introducing a pharmaceutical product into a predetermined emerging market, and details how the framework was applied during an internship at the Genzyme Corporation. The framework includes three steps, as illustrated in Figure 1-2. The first step is market assessment. The second step focuses on the supply chain. Information gleaned from market research is used to propose and evaluate alternative operational structures, to reduce costs, and to facilitate market entry (satisfying regulatory and/or product costs requirements). The third step involves financial modeling. The focus is on analytic tools that explicitly account for uncertainty in the information collected from market assessment and supply chain analysis. The focus of this work is on economic evaluation and risk assessment. We recognize that non-economic, strategic factors can also influence a company's decision to enter a new market, but these factors are not studied in this thesis.

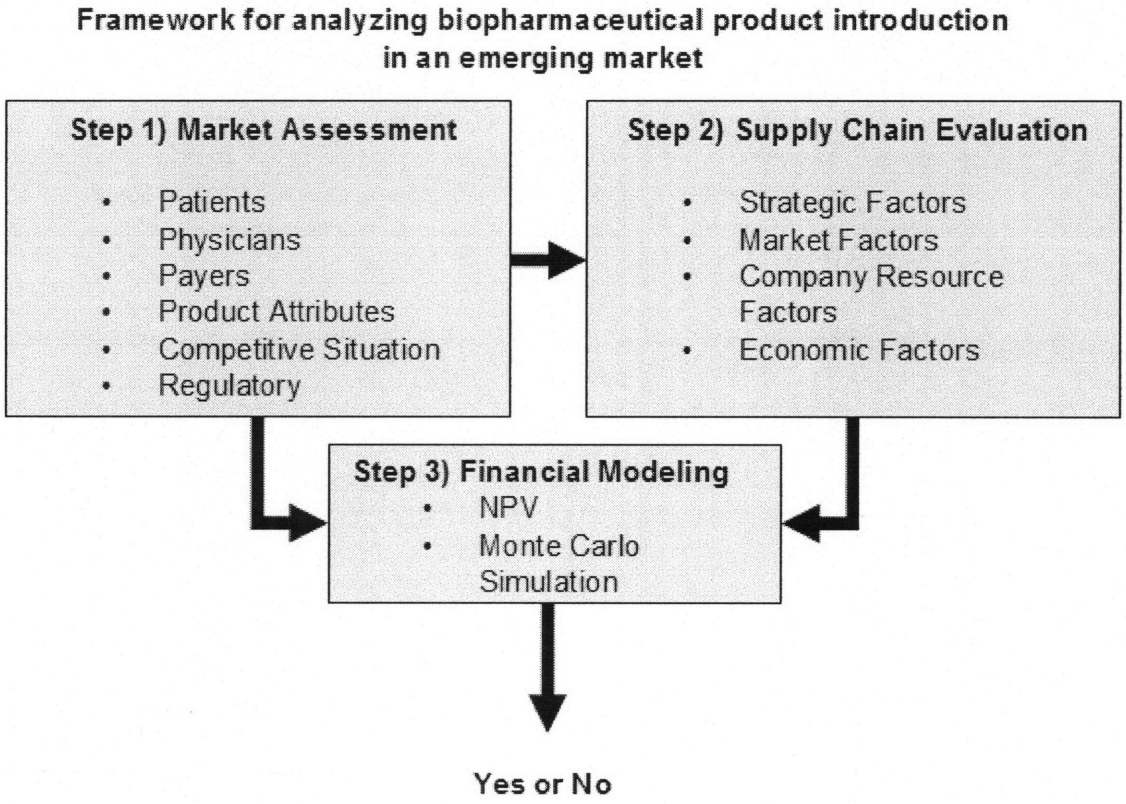


Figure 1-2: Graphical Representation of the Framework utilized for analyzing biopharmaceutical product introduction in an emerging market

1.4 Thesis Overview

The remainder of the thesis is organized as follows:

- **Chapter 2: Overall Market Potential**
  In Chapter 2 we define the six focus areas of market assessment. The information gathered specific to Cholestagel gives a much clearer look at the cholesterol lowering market in China and Cholestagel's product positioning in this competitive environment.

- **Chapter 3: Supply Chain Evaluations**
  Chapter 3 describes the major factors used to assess supply chain alternatives. This includes a look at the firm's internal capabilities, and a comparison with alternatives available in the market place. The chapter maps out the current Cholestagel supply chain and discusses the alternatives considered and eliminated for the China Market.

- **Chapter 4: Financial Evaluation Techniques**
  In Chapter 4, we describe two financial analysis tools typically used in project evaluation and their relative strengths and weaknesses. The main focus will be on Monte Carlo Simulation, a sophisticated technique that allows the user to visually capture the range of outcomes associated with a project. This chapter will show the equation used to calculate expected returns from the Cholestagel venture, speak to the critical assumptions made during equation formulation, and display Monte Carlo simulation results. We wrap up with a final recommendation for the case study examined

2 Market Potential

This framework emphasizes a data-driven approach to evaluating emerging markets. In Appendix A we look at some of the challenges associated with collecting international marketing data, and suggest ways in which to obtain free or low-cost information.

Market research methods fall into two basic categories: primary and secondary. In primary research original data is collected through focus groups, surveys, or one-on-one interviews from current and prospective customers. In secondary research, data is collected from existing sources such as reference books, industry publications, and government agencies.

In assessing the market potential, we adopted an existing product strategy framework developed by Putnam Associates (*4*). Putnam's product strategy framework defines six broad categories: patients, physicians, payors, product, competitive landscape, and regulatory climate. In the context of this thesis, these categories were used to structure the market research and information gathering activities as detailed below. The information gathered through these activities will then feed into the decision making with regards to operations strategy (chapter 3) and provides valuable data to develop more reliable forecast models (chapter 4).

2.1 Patients

Analyzing market potential for a pharmaceutical drug begins with identifying and understanding the patients and their needs. Four key determinants in this category include prevalence, incidence, awareness, and influence. Prevalence gauges the number afflicted with a disease and gives a sense of the market opportunity. The growth rate or incidence of a disease predicts the future market size. In some developing countries, healthcare infrastructure is poor and affects the number of patients who are familiar with or treated for a disease. Awareness rate and treatment rate affect the market opportunity represented by prevalence and determines the importance or need for marketing activity. Finally, who or what influences a patient can help focus the manager's marketing efforts.

2.2 Physicians

When it comes to medical needs, patients will often rely on medical expertise to guide them in their purchasing behavior. Therefore, though patients are the business end consumer, physicians are typically the main customer. It is important to identify what types of physicians (e.g., generalists vs. specialists) patients turn to for a particular disease category. Knowing why doctors prescribe a specific drug, or what characteristics might drive their prescription behavior, may help with developing product messaging. Equally important is learning what mediums physicians often rely upon for learning about new medical products.

2.3 Payors

A major stakeholder in the healthcare system involves the payor. Payors can take various forms including patients that self-pay, patients covered by government insurance schemes, or private insurance systems. If they involve insurance schemes business managers should also understand the characteristics of the different plans offered to most patients. The offered plans may limit the selection of drugs covered based on the value proposition or price. Healthcare can be especially expensive for those battling chronic illnesses. Because each of the insurance schemes affects how much patients end up paying for their healthcare, they may also have a major influence on product choice.

2.4 Product Attributes

Product placement in the new market requires an in-depth understanding of the product technology and relevant history. Business managers must know the product's disadvantages and competitive advantages. This information should allow the firm to understand how the product might meet customer needs or how it can distinguish itself from the competition. Often this combined information can help shape company marketing messages and activities.

2.5 Competitive Situation

The company standing in the market place and the strategic direction undertaken will largely depend on the existing competitive situation as well as future entrants or treatments. A firm must identify local and foreign competitors. If there are competitors, competitor analysis allows a firm to benchmark successful and unsuccessful market entry strategies undertaken by pioneers. The firm may also be able to identify unmet medical needs by assessing the strengths and weaknesses of the competition. The competitor pricing structure will also give insights into supply demand market equilibrium and help a firm choose a pricing strategy.

2.6 Government Policies

The pharmaceutical industry from manufacturing to marketing is entirely affected by government regulations. As a result, success and growth in this industry is heavily influenced by government policies. Import tax laws, pricing policies, or the existence of state-subsidized firms may make it difficult for an entering firm to compete. In developing countries, sometimes it is the lack of policy or limited experience with a new policy, such as intellectual property protection, which makes the market risky for the firm.

Figure 2-1: Market Assessment Focus Areas (*4*)

Focus Areas	Determinants of Value	Description
Patients	Prevalence	Number afflicted with a disease
	Incidence	Additional cases of the disease per time
	Awareness	Familiarity with the disease
	Influence	Who or what can affect the decision making
Physicians	MD Characteristics	The type of physician that typically treats the disease category (i.e., cardiologist, psychologist, dermatologist, etc.)
	Prescription Drivers	The factors that influence the physician's prescription choice
	Usage Pattern	The physician's prescribing tendency, breadth and depth for leading drugs in a class.
	Education/Promotion	Information channels physicians typically rely on for information about new drugs.
Payors	Plan Characteristics	Insurance plan limitations or offerings in the amount or type of medical treatment covered for the patient
	Pricing	Price ranges that payers are willing to accept
	Value Proposition	How does price compare to the product offering
Product Attributes	Relative Positioning	Compare and contrast product to existing treatment options
	Utilization of Positioning Opportunities	How to best market the product's differentiating attributes
	Lifecycle Strategy	How to maintain competitive advantage: New indications, combination therapy usage, etc.
Competitive Situation	Profiles of current players	The current competition and their product attributes, both strengths and weaknesses
	New Entrants/Treatment	New treatments expected to enter the market place prior to product introduction
	Scenario	What different situations may arise
Regulatory	Government Policy	Any policies that govern the industry. (Import tax laws, pricing policies, or the existence of state-subsidized firms)
	Promotional Limits	Limitations on marketing tools: mass media advertising, free product sampling

2.7 China Market Assessment: Cholestagel

The information in the analysis below comes from a variety of sources, including literature reviews, organization-wide interviews and internal resources, and data gathered from primary market research in China detailed in Appendix B.

The Disease: Hypercholesterolemia/Hyperlipidaemia

Hypercholesterolemia/hyperlipidaemia, is a form of lipid metabolism disorder, where overall cholesterol levels in the bloodstream are excessively high. The lipid families of concern include low density lipoproteins and high density lipoproteins. The lipid families are described below.

- Low density lipoproteins (LDL) are a major cholesterol carrier in the blood and are often known as 'bad' cholesterol. High levels of LDL can cause plaque build-up in the arteries leading to a narrowing of blood vessels. Blocked arteries that feed the brain can result in a stroke and blocked arteries that feed the heart can result in a heart attack.

- High density lipoproteins (HDL) carry cholesterol away from the arteries back to the liver where it is excreted from the body. They are often known as 'good' cholesterol because they are believed to slow plaque growth in blood vessels.

The guidelines set out by the U.S. National Cholesterol Education Program (NCEP) for diagnosing the disorder is seen in Figure 2-2.

Total Cholesterol	Category
< 200 mg/dL	Desirable
200-239 mg/dL	Borderline High
> 240 mg/dL	High
LDL Cholesterol Level	**Category**
< 100 mg/dL	Optimal
100-129 mg/dL	Near optimal/above optimal
130-159 mg/dL	Borderline High
160-189 mg/dL	High
> 190 mg/dL	Very High
HDL Cholesterol	**Category**
< 40mg/dL	Risky
> 60 mg/dL	Desirable

*Cholesterol levels are measured in milligrams of cholesterol per deciliter of blood

Figure 2-2: NCEP Guidelines for Cholesterol Diagnosis (*5*)

Patients

Prevalence & Incidence

Hypercholesterolemia is a disorder that typically affects developed countries. Table 2-1 shows the prevalence rate in seven major pharmaceutical markets and compares that with prevalence in China. Hyperlipidaemia affects over 100 million people in China, which is over twice that in Germany and about 80% of that in the US. As China becomes more industrialized, we expect this number to rise rapidly, especially in the urban population.

Table 2-1: Prevalence of Hypercholesterolemia (*6*)

	China*	US	Japan	France	Germany	Italy	Spain	UK
Prevalence (million)	**117.3**	142.2	25.7	30.9	53.8	19.8	9.0	31.3
Rate (%)	**9**	49	20	52	65	35	23	53

In Figure 2-3 we see that 68% of hyperlipidaemia cases in China are in the borderline risk category for the disorder. This group requires 23% to 38% lipid lowering to reach the optimal

LDL level of <100mg/ml as defined by the NCEP. Only 11% are in the very high risk category and these patients would require over 50% lipid lowering to reach optimal LDL levels.

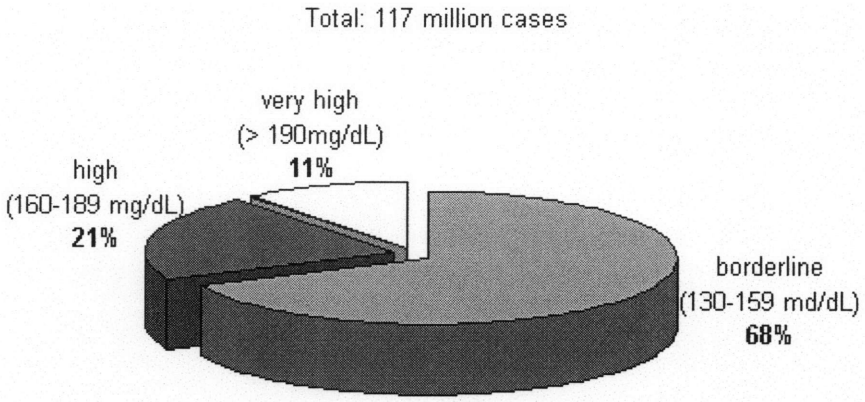


Figure 2-3: Breakdown of Hyperlipidaemia Cases in China (*7*)

Influence

In the past, the government's control over advertising of medical products in China was lax, with Chinese manufacturers often making extravagant claims for products. Since 2001, under new regulations, advertising of prescription drugs in the mass media has been banned and is only permitted in approved medical and trade journals (*8*). Without the direct to consumer marketing of pharmaceuticals products in China, patients will more likely rely on their physicians for medical advice.

Physicians

Prescription Driver

The vast majority of all medical benefits are provided through hospitals and other health care facilities. The public hospital sector is segmented into 3 tiers:

- Tier III: Academic/Medical; highest level
- Tier II: Smaller Cities
- Tier I: Rural Communities; lowest level

In the 16 major urban cities, patients typically go to Tier III (top level hospital) for treatment, and then perhaps to a Tier II for follow-up, but continue with the prescription handed out from a Tier III level physician (*9*). Therefore to be cost efficient, branded pharmaceutical products should focus marketing/sales efforts to the Tier III and Tier II hospitals.

Over the years, because of low government funding, hospitals support themselves through the sale of prescription products. As a results, pharmaceutical sales at hospitals account for a little less than 80% of the pharmaceutical market, Figure 2-4. It is important to gain support from doctors in the hospitals because they affect what drugs are carried in the hospitals. Based on our market research, we also found that doctors take into considering drug reimbursement when they prescribe drugs.

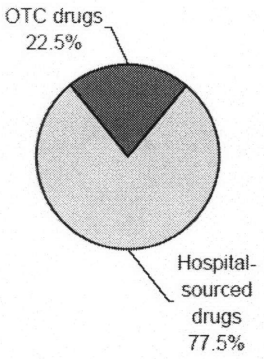


Figure 2-4: Pharmaceutical Market Sector in 2004 (*10*)

Education & Promotion

Promotional efforts should be focused on the 3 main channels doctors listed during our market research as their sources for new product information (Figure 2-5)

- Medical Journals (89% of doctors interviewed use this type of education channel)
- Symposium (85%)
- Company Representative Introduction (63%)

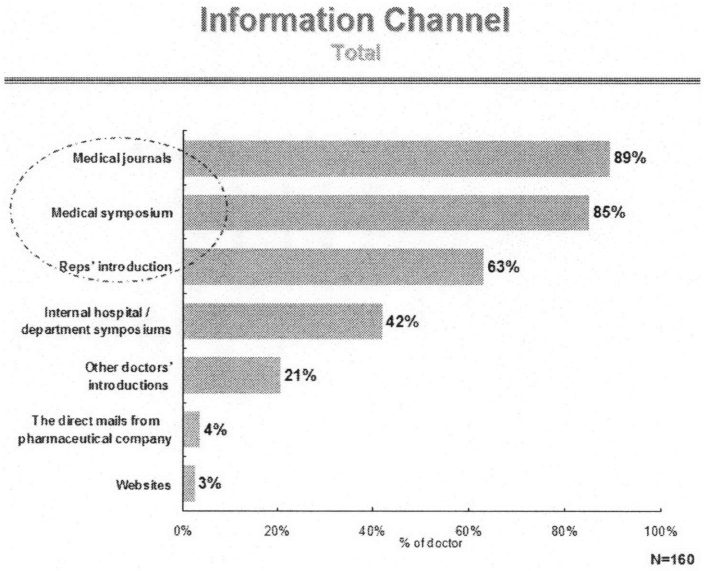


Figure 2-5: Information Channels Typically Utilized by Physicians

Payors

In China, there is a significant income disparity between the urban and rural areas. Though China's population stands at approximately 1.3 billion, the affluent population represents only about 10% of that and is concentrated along the eastern region of the country in 16 cities:

Beijing, Chengdu, Chongqing, Dalian, Guangzhou, Haerbing, Hangzhou, Tianjin, Shenyang, Shanghai, Qingdao, Nanjing, Ji'nan, Wuhan, Xi'an, and Zhengzhou.

In addition to the income disparity, there is a huge disparity in access to healthcare and insurance. The Chinese Government switched from a free health care system to a partial provider-pay system in the late 1990s as part of their political-economic transition to a free market economy. As a result, China's large rural population could no longer afford healthcare, and many were forced to pay for the major share of their medical services out of their own pockets. Therefore, purchasers in China are extremely price sensitive. In the urban areas, insurance schemes do exist. The Ministry of Labor and Social Security delegated responsibility for implementing an insurance scheme to regional administrations, and therefore schemes differ from region to region.

Reimbursement (*7*)
A patient can only be reimbursed for drugs listed on the insurance system reimbursement list. The national reimbursement list is controlled by the central government. However, each of China's provinces (regional governments) will have its own list to suit the particular needs of its province. For most provinces, a drug will only qualify onto the reimbursement list after it has been on the Chinese market for 2 years and has proved to be cost-effective. Each province may require additional price reduction from the market entry price in order for the drug manufacturer's drug to be approved for the list.

Genzyme's Cholesterol Lowering Agent: Cholestagel

Cholestagel, colesevelam hydrochloride, is a specifically engineered polymer based bile acid sequestrant used to treat hypercholesterolemia. It is currently approved in the U.S., and was successfully marketed there by Sankyo U.S. under the brand name WelChol since 2000. WelChol is the highest selling bile acid sequestrant on the U.S. market with sales of approximately $170 million per year for the treatment of hyperlipidaemia.

Below we discuss some of the key advantages and disadvantages that were noted during our primary research in China, see Appendix B for more details.

Advantages

- Effective as Combination Therapy (41% of 160 physicians interviewed)
  Co-administration of Cholestagel and a low dose statin has been shown to provide LDL cholesterol lowering beyond using either therapy alone. 41% of the physicians saw combination therapy as a product advantage. Honghui Medicines acknowledged that more and more doctors are becoming interested in combination therapy drugs (*11*).

- Non-systemic mode of action (34%)
  Hepatitis B, a disease of the liver, is a large problem in the Chinese market with over 100 million people chronically affected (*12*). Cholestagel lowers LDL-C levels without entering the circulatory system. In contrast to statins, at no time does the product enter or

act on the liver or kidneys and no liver function monitoring is required of patients on Cholestagel. 34% of physicians noted this as a key advantage of the product.

- Side effects (26%)
  In 2001, Bayer's statin product Lipobay was pulled from the market after a number of deaths occurred when the drug was combined with gemifibrozil. The bad publicity surrounding the deaths increased doctors' concerns about the side effects of high does of statins.

Disadvantages

- Big Tablet/Poor Patient Compliance (21%)
  Physicians typically prescribe 10mg statins to their patients. The Cholestagel treatment regiments require patients to take six 625mg tablets every day, or over 300 times the daily load of a statin. This large tablet load may not be well tolerated by older patients and is an additional burden to patients who have other medicinal requirements.

- Monotherapy not as effective as competitor product (21%)
  As a monotherapy, Cholestagel has been shown to lower LDL cholesterol on average 15-18%. Though this LDL lowering will be sufficient for those with borderline cholesterol risk, it is not as effective as a 10mg dose of statin which in the case of atorvastatin (generic form of Pfizer's Lipitor) has been shown to lower LDL cholesterol on average 39% (*13*).

- High Price (16%)
  A daily dose of Cholestagel is more expensive to produce than a daily dose of statin, in part because of the sheer quantity of the drug that needs to be consumed. In the U.S. it has commanded a price premium above most statins because many patients who cannot tolerate statins will turn to it as an alternative treatment. In China, those who cannot tolerate statins will turn to Traditional Chinese Medicines, TCMs, which cost less than 15 cents for a daily dose. Unless the drug can be reimbursed through insurance, the high price of the treatment will mean that only those with a high income level can afford the drug.

Anti-hyperlipidaemia market

Market Size (*14*)

In the U.S., the hyperlipidaemia market in 2005 was approximately $15.5 billion. Based on the sheer number of hyperlipidaemia cases seen in China (similar numbers to the U.S.), we would have expected a very sizable anti-hyperlipidaemia market. However, IMS (company that specializes in the collection of health information) data analysis shows that the entire China hyperlipidaemia market in 2005 was $92 million ($54 million for 16 major urban markets), with a little over 0.77 million patient cases. The market had impressive growth of 28% in 2004 and again in 2005, Table 2-2.

	US	China
Statistical Prevalence (2004)	142 m	117 m
Hypercholesterolemia market (2005)	$15.5 bn	$92 m
CAGR% est	5%	28%
Cholestagel/Welchol Revenue (2005)	$170 m (1.1%)	n/a

Table 2-2: Anti-hyperlipidaemia market in the US and in China

Based on IMS data, combined with conversations with persons experienced with the sales of hyperlipidaemia drugs in China, we expect continued rapid growth in this market. In Figure 2-6, we see the projected market size for 16 major urban markets through 2014 (patent life of Cholestagel) assuming 30%, 40% and 50% growth. Even with 50% growth for the next 8 years, the market stands at only $2.1 billion or less than 20% of the 2005 U.S. hyperlipidaemia market.

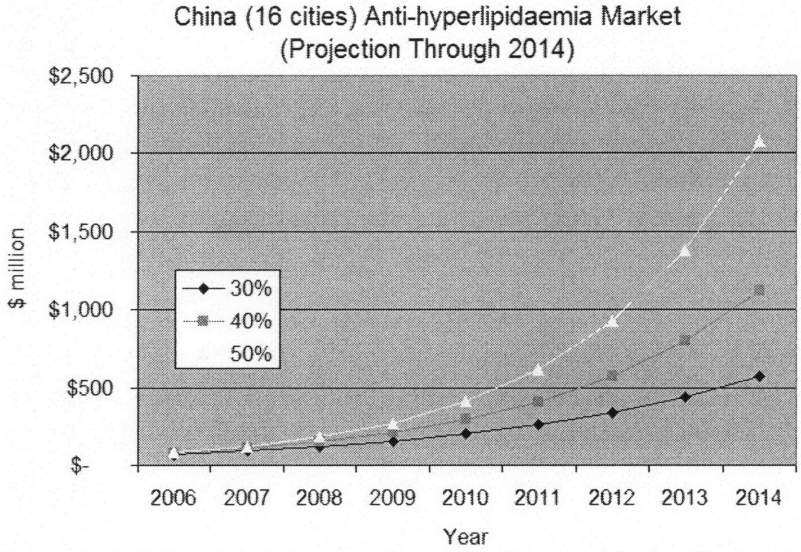


Figure 2-6: China 16 cities Anti-hyperlipidaemia Market Projection
IMS Data: China Market

Competitive Landscape

The hyperlipidaemia market in China is crowded. All major anti-hyperlipidaemia brands have been introduced in China including zocor®, lescol®, pravachol®, mevalotin®, and most recently lipitor®. For each of these brands, the average retail daily dose (averaged across different available dosage) is priced below $1, Table 2-3. Cholesterol drug regulators are often categorized based on their mechanism of actions. In China, these categories include statins, fibrates, and others (nicotinic acid, probucol, and pantosin). Cholestagel belongs to a class called Bile Acid Sequestrants (BAS).

Statins	avg unit price	~of patients	2005 mkt (million)	mkt share	2003 world mkt (million)
zocor (merck)	$ 0.88	50,571	$ 16	23	$ 5,000
lipitor (pfizer)	$ 0.89	45,766	$ 12	19	$ 9,200
lescol(Novartis)	$ 0.54	36,877	$ 7	10	$ 700
pravachol (Squibb)	$ 0.91	16,021	$ 5	8	$ 2,800
mevalotin (sankyo)	$ 0.60	14,966	$ 3	5	$ 1,800

Table 2-3: Market Information on major anti-hyperlipidaemia brands in China (14, *15*)

Current Treatments

- **Statins:** Well established and is the first line of treatment for hyperlipidaemia
- **Bile Acid Sequestrant:** Is quickly being phased out from treatment and invokes many negative comments (old drug, GI side effect, limited effect of lowering LDL).
- **Traditional Chinese Medicine (TCM):** 19% of patients with liver disorders are treated with TCM. TCMs are very inexpensive (<15 cents/daily dose).

New Entrants

- **Zetia®:** Schering Plough's Zetia® completed phase III clinical trials at the end of 2005 and is expected to launch in China in mid-2006. Schering Plough has undertaken large marketing efforts to differentiate itself as an alternative to statins because it acts in the intestines rather than the liver. Though Cholestagel® operates under a different mechanism, because it too acts within the intestines, it will be inevitably compared to Zetia® who gains a competitive advantage from being first-to-market and its small tablet size of 10mg.

Regulatory

Government Policies

China entered the World Trade Organization (WTO) in 2001 and agreed to government policy changes which would improve market access and allow for a more competitive environment. Below is a look at some of the pharmaceutical-related regulation changes:

- **Strengthened Patent Protection:**
  China will conform to a patent protection structure similar to the U.S. Patent legislation, granting 20 year protection. The protection extends to substances, applications, and manufacturing.

- **Tariff Relaxation**
  Import duties were reduced 60% in 3 years starting in 2001, from 9.6% to 4.2%, to be more in-line with developed countries. This applies to bulk pharmaceutical substances and finished products.

- **Distribution**
  Foreign manufacturers will be allowed to sell directly to wholesalers and retailers. They will also allow for more foreign ownership of the wholesaling and retailing business.

Weaknesses in the System

China's economy and government policies can best be described as in flux. The market environment has seen much improvement but implementation of WTO policies has been slow and requires monitoring by the industry. Some of the issues that exist include:

- **Lengthy approval process: Registration (*16*)**
  The Registration process from filing to government market sale approval will take 2-2.5 years in China compared to 1-1.5 years in the U.S., Europe, and Japan. The delay in processing comes in part because local clinical trials are mandatory for all drugs new to the Chinese Market, even for drugs which have already gone through clinical trials in other geographic regions.

- **Protection of Intellectual Property:**
  The concept of patent protection and intellectual property rights is fairly new to China. As a result, there is a lack of enforcement of patent legislation, and penalties are often very low.

- **Discrimination against foreign makers**
  Many domestically produced pharmaceuticals do not comply with good manufacturing practices (GMP) standards observed in developed countries. Drug reimbursement policies are also complex, where negotiation is required on a province by province basis. Imported drugs are also often excluded unless the manufacturer agrees to large price cuts.

Key Take-Always

Focus Areas	Take-Aways
Patients	There are over 100 million people in China with hyperlipidaemia, 80% the prevalence in the U.S. As China becomes more industrialized we expect this number to rise rapidly, especially in the urban population
Physicians	Most patients go to hospitals to fill their prescription drug needs. Therefore, it is important to gain support from doctors in the hospitals because they affect what drugs are carried in the hospitals.
Payors	In China, there is a significant disparity in access to healthcare and insurance. Therefore, purchasers in China are extremely price sensitive. Patients can only be reimbursed for drugs listed on the insurance system reimbursement list. Drugs need to be on the market for two years before they can be added to a reimbursement list.
Product Attributes	40% of the physicians interviewed were most interested in Cholestagel as a combination therapy and over 30% believed that its non-systemic mode of action was a key advantage. Physicians felt that the big tablets would not be tolerable to older patients and therefore affect compliance. They also felt that Cholestagel was not as effective as existing drugs as a monotherapy.
Competitive Situation	In China, the hyperlipidaemia market in 2005 was $92 million with growth rates of 28% for the past two years. Many of the major anti-hyperlipidaemia brands have already been introduced at an average retail daily dose below $1. Cholestagel will likely be compared to Zetia, which Schering Plough will introduce into the China market in mid-2006.
Regulatory	Government policies are changing slowly to conform to WTO policies. However, the three year drug approval process is long by western standards, intellectual property protection is still lax, and drug reimbursement policies favor domestic drugs.

3 Supply Chain Evaluation

Market assessment alone is not enough to determine if it is financially sound to bring a pharmaceutical product to a market. The second important step in the analysis focuses on the supply chain. Supply chain evaluation takes into account four main factors: strategic factors, market factors, company resource factors, and economic factors (Figure 3-1) (*17*). In this chapter we will discuss these factors generally, and then consider them in detail for Genzyme's product in China.

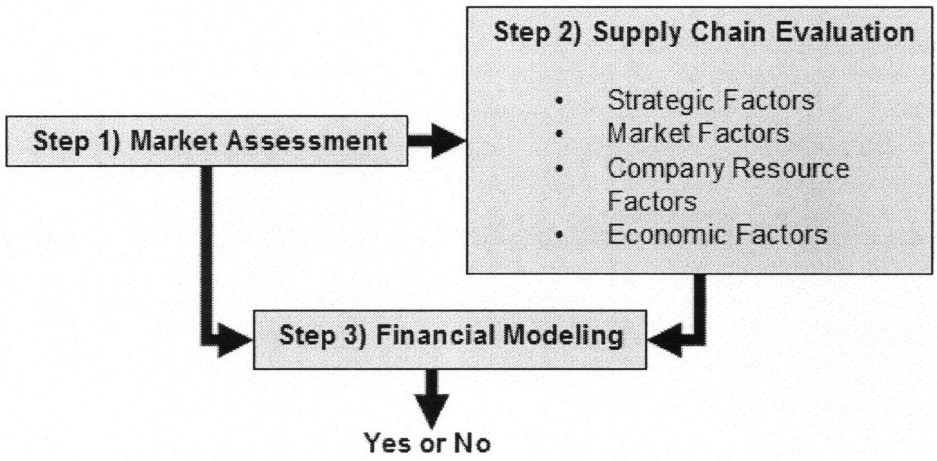


Figure 3-1: Four key factors to supply chain evaluation

3.1 Strategic

Evaluating supply chain options often starts with weighing alternatives against the firm's overarching strategy, overall objective. In some cases, an alternative may be more costly, but is worth fully examining because it is a strategic fit. Another important part of the strategy is determining what type of supply chain will be needed to support the business. An efficient supply chain is more suitable to support stable products whereas a responsive supply chain better supports innovative/rapidly changing business (*18*). In the case of biopharmaceutical products, an efficient supply chain will often be more appropriate. Though the market demand may be uncertain before market entry, after market entry these products usually have predictable product life cycles. Some of the questions that should arise include:

- What is the firm's overarching strategy and what level of risk is the company willing to accept inherent in emerging markets.
- Evaluate the strategic needs of the supply chain.
- Will the option facilitate market entry, time-to-market, or market access?
- Can future products benefit from this option?
- Will this bring intangible benefits like experience and brand recognition?

3.2 Market

Market factors take into account industry and country dynamic as assessed in Chapter 2. A company will often leverage external resources (suppliers, distributors, and local partners) within the target market in an effort to lower costs and also mitigate risks. The company may benefit from the external resource's unique expertise and knowledge of the target market. However emerging markets often lack regulatory systems or contract-enforcing mechanisms which affect accountability and reliability of the source. In addition, the local infrastructure including road systems, railroads, airports, may not be able to support the firm's distribution of the product. This may be especially critical for biopharmaceutical products which are temperature-sensitive. Finally, it is helpful to understand the skill and expertise of the local partner as this will affect the firm's level of future involvement. For example, firms in western markets have a lot of experience in strategic marketing of branded products using direct-to-consumer advertising and conducting doctor/hospital visits. This same level of marketing experience is not commonplace in emerging markets where a majority of the sales products are generic or copy-cat drugs and do not require a high level of marketing sophistication. These questions may be summarized as follows:

- Are there external sources available in the market of interest?
- Can we be assured that the alternative meets quality, supply, and regulatory requirements?
- Do local partners have the skill and expertise to fully support the brand?

3.3 Company Resources

A firm will need to choose its level of direct involvement based on assessing its internal resources and in-house capabilities. These company resources include financial, technological, production and marketing capabilities. Capital investments differ depending on the company's level of involvement, i.e. exporting vs. in country manufacturing. As a result, the company must make a reasonable decision about the amount of capital investment it can and is willing to make in the emerging market. Information systems and information technology resources are also critical to managing different components of the supply chain. Indeed, researchers have identified information sharing as a critical aspect to operating extended supply chains (*19*). In some cases firms can leverage existing production capacity to meet the demand needs of the new market environment. Additional questions that may arise include:

- Are resources sufficient to meet short term and long term supply needs.
- Do we have existing contracts with external sources?
- How will the different links within the supply chain work together?

3.4 Economic

The economic factor is another key component in evaluating supply chain alternatives. How a product is produced, who produces the product (internal vs. external sources), and where it is produced will affect its costs of goods. Coordination costs associated with running remote operations can be substantial and should be accounted for in any economic model. In emerging

markets, the purchasing power of patients, governments, and healthcare organizations is often low, which may hinder a company's ability to set a high sales price. As a result, the cost of goods relative to market price is usually much higher than in traditional markets and this will in turn affect company profits. However, as mentioned earlier, a firm may still decide that the strategic factors outweigh the economic factors. Additional questions that may arise include:

- How long does it take to ramp up to production?
- Are there tax benefits with any of the alternatives?
- Can costs be mitigated by existing sales or future sales?
- Will the economics change if product volumes change?

3.5 Cholestagel Supply Chain Evaluation

WelChol Supply Chain

Cost of Goods Relative to Market Wholesale Price

In Figure 3-2, we plot the cost of goods (raw material through tabletting) for WelChol against the U.S. and (estimated) Chinese wholesale price. Considering the current cost structure, it is doubtful that sales in China can be profitable. Therefore, it is important to look for alternative supply chain structures that might lower the cost of goods for the China market.

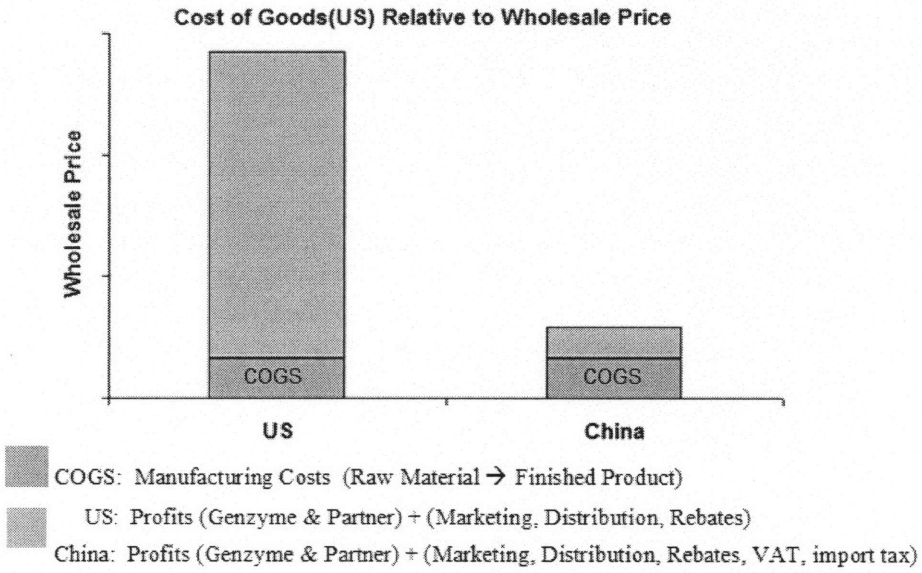


Figure 3-2: Cost of Goods for WelChol relative to US and (estimated) China Wholesale Price

Figure 3-3 details the WelChol supply chain from Raw Material production to Marketing & Sales for the U.S. market. It includes a material flow diagram and material ownership information. The supply chain involves four contract manufacturers located in four different

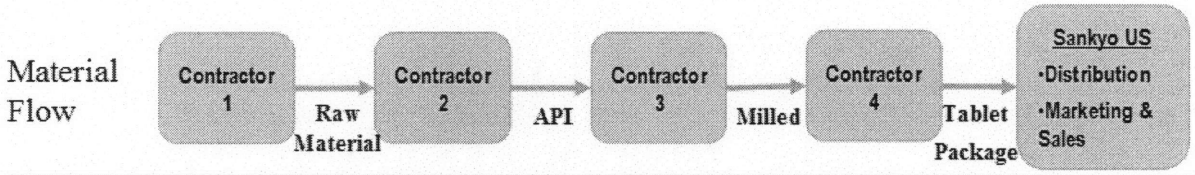
countries. Genzyme does not make any portion of the product in-house and adds minimal overhead cost to the final product. The company has 3 notable contracts:

- ***Genzyme & Contractor 1 (Cambrex)***
  Cambrex supplies raw material for both Genzyme's Renagel and WelChol products. Genzyme directly purchases the raw material for the manufacturing of Renagel. DSM (Contractor 2) purchases the raw material for WelChol on behalf of Genzyme, at rates negotiated in the contract between DSM and Genzyme.

- ***Genzyme & Contractor 2 (DSM)***
  DSM purchases raw material from Cambrex as specified by the contract described above and turns this material into a bulk polymer also known as active pharmaceutical ingredient, API. DSM sends the bulk polymer to Contractor 3 (Powder Size) to mill/grind down to finer particles. Genzyme purchases the milled API (ready for tabletting) from DSM at a set contract price, and only interacts with Powder Size to control inventory levels.

- ***Genzyme & Sankyo U.S.***
  Sankyo purchases the milled API from Genzyme for a set contract price, not necessarily for the same price Genzyme buys milled API from DSM. Sankyo takes the milled API through tabletting, distribution, and finally marketing & sales.

Below we take a closer look at the main components of the supply chain and evaluate a number of options considered for the China Market.



Supplier	•Cambrex	•DSM	•Powder Size	•Patheon	•Sankyo
Location	•Iowa & Sweden	•Linz, Austria	•Quakerstown, Pennsylvania	•Toronto, Canada	•Parsippany, New Jersey
Contract length with Genzyme	•2006	•2014	•Warehouse contract	•No Relationship	•2014

Ownership	Contractor 1	Contractor 2	Genzyme	Sankyo US

Figure 3-3: WelChol Supply Chain

Evaluating Alternative Structures

Raw Material: *The bulk polymer Poly(allylamine hydrochloride) is the main ingredient in Cholestagel.*

Current

Cambrex is contracted to supply raw material for both Genzyme's Renagel and WelChol products. WelChol utilizes approximately 5% and Renagel accounts for 95% of the total raw material ordered. In the case of WelChol, contractor 2 (DSM) purchases the raw material directly from Cambrex at the rates negotiated in the Genzyme contract. Poly(allylamine hydrochloride), PAA, production requires low technology and all patents for this process have expired.

Discussion

The contract with Cambrex expires in 2006. As a result, Genzyme's Operations team is investigating whether to purchase the raw material from another source or to manufacture it in-house. Renagel is Genzyme's second highest revenue generator, and uses a majority of the PAA. The lowering of PAA costs will directly impact Renagel's cost of goods. For WelChol, Genzyme does not have a direct contract with Cambrex, only a contract for the purchase of milled API with DSM. Lowering of PAA costs will only impact WelChol's cost of goods if Genzyme renegotiates with DSM to take over purchasing PAA. Genzyme has taken proposals from a variety of sources including a number of Chinese suppliers. As of November, proposals from a number of European sources have been significantly cheaper than both in-house manufacturing options and proposals from Chinese manufacturers.

Recommendation

The Chinese government is interested in courting foreign direct investments that may bring in a high level of technology into the country (*20*). Because PAA production is a low technology process there may be low strategic benefits in setting up this type of manufacturing production in the country. In addition, based on current proposals, such a move would likely increase raw material costs for Genzyme's second highest product revenue generator, Renagel.

Active Pharmaceutical Ingredient (API) Production: *API is the chemical entity that causes the therapeutic response. In Cholestagel production, poly(allylamine) hydrochloride (PAA) undergoes a cross-linking procedure with another chemical entity in a 12-step process to form the active ingredient colesevelam hydrochloride.(Also known as bulk polymer)*

Current

API production contributes 65% to the COGS of Cholestagel, and is the most complicated of this drug production process. Genzyme negotiated a new contract with DSM in late 2004 giving DSM API production rights until 2014, the year in which the patent of the product ends. With this new contract Genzyme will receive a significant discount on API as order volumes increase. Genzyme owns capacity at DSM that is significantly underutilized. The U.S. market demand has not lived up to the forecast due to increased market competition and as a result, the facility is only operating at 25% of its capacity. If it can increase utilization of that equipment, it will be able to allocate the fixed costs over higher volume, thus reducing per unit costs.

Discussion
There are a number of major hurdles that prevent Genzyme from moving API production to China. Because intellectual property (IP) protection in China is still in the early stages of development, there is much reluctance on the part of Genzyme's executives to hand over key process information. Any unexpected delays or complications during transition to a Chinese manufacturer could also affect Genzyme's relationship with its U.S. partner Sankyo. Finally, estimated product sales in China do not warrant buying out the DSM contract or affecting relationships with Sankyo.

Recommendation
Genzyme's management team wants minimal investment and minimum risk while entering China with Cholestagel. Therefore, Genzyme should maintain its current relationship with its API suppliers. At this time, Genzyme would not be able price Cholestagel at a competitive price unless it applies the API volume discounts entirely to the China market. However, Genzyme should be aware that Sankyo may also want to share in the increased profits as volume increases.

Milling: *The bulk polymer of API, colesevelam 10 mesh, is pulverized into fine particles, colesevelam 80 mesh. The particles undergo a sieve analysis in order to measure the particle size property.*

Current
Genzyme has no existing contract with the milling company, Powder Size. The API manufacturer, DSM, owns a contract with the milling company. Estimates place milling costs at about 2% of fully loaded cost of goods.

Discussion
There appears to be no large value or immediate reason to find an alternative milling source if Genzyme chooses to buy out its contract with DSM. The milling process is not a high technology process and would be unlikely to aid market entry because it is not viewed by the Chinese government as a value-adding technology. In addition, the milling cost represents a small portion of the entire costs. Therefore, efforts to reduce overall cost of goods should be focused on higher value pieces of the supply chain.

Recommendation
Maintain current relationship

Tabletting: *The milled API is processed with a number of excipients in a series of steps before it is compressed and film-coated into a tablet. Each tablet contains 625mg of API. Excipients are inert substances that act as fillers and aide in the delivery of a drug. Finished tablets are then packaged in high density polyethylene bottles. Every lot of Cholestagel tablets then undergoes a number of quality and stability tests.*

Current
Sankyo owns the milled WelChol product once it arrives at the Sankyo contract tabletting facility, Patheon. Genzyme does not know the exact tabletting costs associated with making

WelChol. However, they can estimate these costs based on tabletting experience with Renagel. Initial estimates place tabletting at 20-25% of the entire cost of goods (assuming no API discounts).

Discussion

A number of alternatives were considered for the tabletting of Cholestagel for the China market, Figure 3-4. We evaluate each scenario below

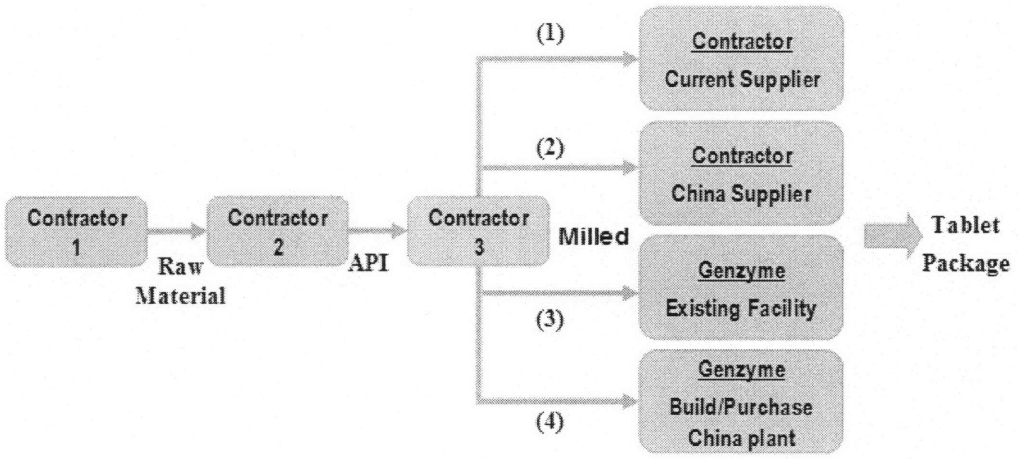


Figure 3-4: Tabletting production alternatives

1) **Use Sankyo's tabletting source, Patheon.**
   Since Cholestagel tabletting should be no different from WelChol tabletting except for the finished stamping of the drug name on each tablet, it would make sense to turn first to Patheon as a viable tabletting source. Patheon has experience with the process and therefore Genzyme would not need to go through the learning period required when setting up a new process. Additionally, Genzyme would only need to purchase a minimum amount of equipment, and therefore take a smaller financial risk. Sankyo provided initial estimates that show tabletting costs will only be half the cost estimated with tabletting at an existing Genzyme facility, Option 3. Tabletting costs may be much lower than Genzyme facility because Cholestagel tabletting is only being charged incremental costs and not overhead costs.

2) **Contract tablet in China**
   Management was concerned about the lax IP protection in China and did not want to send out process information for pricing purposes. However, a number of firms we visited in China indicated they have modern tabletting capabilities and have invited Genzyme to visit these facilities on future visits. Genzyme plans to investigate this option if the company decides to take Cholestagel into the China market.

3) **Use existing Genzyme tabletting capacity**
   Genzyme's tabletting site in Waterford, Ireland has enough capacity to take on Cholestagel tabletting. However, the equipment is build for Renagel tabletting, slightly

different from Cholestagel tabletting. Genzyme would need to make a $1 million investment in new quality control equipment and modification of existing equipment. Finally, due to Genzyme's accounting treatment of overhead costs, Cholestagel would have to bear some of the overhead costs that are largely due to Renagel tabletting, thus reducing any cost benefits that might be achieved due to economies of scale. Of course, this would help Renagel, as its overhead would go down.

4) **Setting up tabletting facility in China**
Investing in a new plant in China would only make economic sense if the facility could also be used to tablet other products. The start-up costs for a new plant are far too high for Cholestagel to bear alone. However, Genzyme's current product portfolio is highly diverse and the only other product that could utilize such a facility is Renagel. Renagel already has a Genzyme-own dedicated tabletting site in Waterford and moving tabletting to China could be very costly considering the substantial fixed costs invested in this existing plant.

Recommendation
The lowest investment and least risky option is Option 1: to use Sankyo's tabletting source. Because many of the companies we spoke with have tabletting capabilities Option 2 also remains an open possibility, but it would require executive level support.

Distribution: *Sankyo U.S. is the sole distributor of WelChol and is responsible for providing the product to hospital systems, physician's office, mail order facilities, and independent pharmacies across the U.S.*

Current
At this time, Genzyme does not have its own distribution channels within the country.

Discussion
The pharmaceutical distribution system in China is extremely competitive and highly complex. It is a multi-level (tiered) system consisting of national suppliers, hundreds of provincial/regional wholesalers, and thousands of local distributors (different from Hospital Tier I, II, III). Since most distributors cover only a small area of the country, a company seeking broad geographic coverage will need to utilize a large number of distributors (*21*). In an attempt to reform the drug distribution system, the Chinese State Economic Trade Commission is starting to allow multinationals to participate in establishing pharmacy chains and delivery centers. Since Genzyme is so new to the Chinese market it seems most reasonable to rely on a company that can navigate existing distribution networks rather than risk entanglement in this complex system. Early discussions place distribution margins at around 5%-10% of retail price for each tier, and there may be multiple tiers.

Cholestagel is a branded pharmaceutical product with cost of goods higher than the retail price of most generic statins on the current Chinese market. Therefore, Cholestagel sales will most likely be limited to the affluent. In addition, as we learned from market research (Chapter 2), patients typically go to Tier III or Tier II hospitals for treatment and the purchase of pharmaceutical

drugs. As a result, Genzyme will need to find a distributor with high penetration of Tier III and Tier II hospitals in the 16 major cities.

During discussion with distributors in China, we learned that for highly competitive products, distributors have to go through a bidding process in order to get their products into the hospital pharmacy. In this bidding system wholesalers selling drugs in the same class enter into a bidding war to gain 1-2 years exclusivity to supply to the hospital pharmacy. More hospitals are participating in the bidding system to get distributors to provide deep discounts which are leading to increased hospital margins on the sale of prescription drugs. The details of this bidding system are not entirely clear to this author nor is it clear whether Cholestagel would have to compete in such a process. However, more and more distributors are touting their ability to enter successful bids. This topic warrants further investigation in the event Genzyme decides to take Cholestagel to this market.

Recommendation

The pharmaceutical distribution system is far too complex and far too competitive for Genzyme to go into alone. Since Genzyme is new to this market, the least risky option is to rely on a company that can navigate the existing distribution networks. Early discussions place distribution margins at around 5%-10% of retail price for each tier, and at least three tiers may be involved (*22*). A distribution partner should have broad coverage of Tier III and Tier II hospitals in the 16 major cities of China.

Marketing & Sales: *Sankyo U.S. has a sizable group of sales representatives that call upon physicians regularly providing information (pamphlets/brochures) and free drug samples.*

Current

Genzyme has no marketing or sales force in China. The marketing sales force at Sankyo has experienced a direct link between increased marketing efforts with increased WelChol sales.

Discussion

Based on market research, physicians are linking Cholestagel to an older version of bile-acid-binder which has poor efficacy and tolerability. These preconceptions highlight the need to find a strong marketing partner who can clarify the mechanism of Cholestagel to differentiate it from the traditional bile acid binders and existing competition. This product will not sell if partners distribute this product without a strong message. However, finding a strong marketing partner in China may be difficult because Chinese companies often do not have this area of expertise (*19*). As a result, Genzyme should expect to be more involved with promotion and marketing than would normally be required in traditional markets.

The advertising of prescription drugs in the mass media has been banned; advertising is permitted only in approved medical and trade journals. As a result marketing efforts focus primary on physicians and not on the consumers (patients). Our market research shows that physicians learn about new product information from medical journals (89%), medical symposiums (85%), and visits from company representatives (63%). The ideal partner would have access to all three information channels.

Genzyme's ideal marketing partner for Cholestagel would have an established Cardiovascular Disease Group, CVD, with a strong sales force and access to medical experts to attend symposiums. This situation would be beneficial for both Genzyme and the partner. From Genzyme's perspective, Cholestagel could more quickly reach peak sales because it would have immediate access to a large network of doctors and hospitals. From the partner's perspective, because it has existing sales representatives dedicated to this disease group, the company can increase its product offering/sales without having to significantly increase costs. In fact, one generic statin marketer expressed interest in Cholestagel as an add-on therapy to statin and did not see Cholestagel as a direct competitor. This was an opportunity to meet the needs of physicians interested in combination therapy treatment of hyperlipidaemia.

Marketing costs are likely to be high and market share is likely to be low for the first two years that Cholestagel is on the market or at least up until Cholestagel is placed onto the drug reimbursement list. It is still unclear what percentage of the retail price will go towards marketing. Initial estimates range anywhere from 10% to 50% of retail price (11).

Recommendation
Genzyme needs a strong marketing partner who can help clarify the mechanism of Cholestagel and differentiate it from the traditional bile-acid-binders. The ideal marketing partner would have an established Cardiovascular Disease Group with resources to reach physicians in the office, through medical journals, and at medical symposiums. Genzyme should expect marketing costs to be significant while Cholestagel is not on the drug reimbursement list.

3.6 Recommended Supply Chain For Cholestagel China Market Entry

Table 3-1 below summarizes the supply chain recommendations discussed in this chapter. Aside from API volume discounts being applied to Cholestagel for the China market, we were unable to find additional cost savings through changes in the supply chain from Raw Material production through Tabletting. The economics associated with the following recommendation will be added into the financial evaluation model discussed at length in Chapter 4.

Table 3-1: Summary of Supply Chain Recommendation.

Summary of Supply Chain Recommendation	
Raw Material	Assume same supplier and cost structure (may change depending on results from Renagel investigation)
API	Maintain same supplier. All volume discount applied to China market.
Milling	No change (linked directly to API evaluation)
Tabletting	Use Sankyo's tabletting source
Distribution	Form JV with distributor in China (focus on 16 major cities)
Marketing	Find strong marketing partner with experience in CVD

4 Financial Evaluation Techniques

The third step in the framework (Figure 4-1) for analyzing pharmaceutical product introduction in an emerging market involves financial modeling. The information from market assessment (Chapter 2) and the cost component from our supply chain analysis (Chapter 3) are developed into a financial model for final project evaluation. In this chapter we take a closer look at two available financial analysis tools typically used in project evaluation: Net Present Value (NPV) and Monte Carlo Simulation (*23*). However, the main focus will be on Monte Carlo Simulation, a sophisticated technique that allows the user to explicitly account for uncertainty in the information collected from market assessment and supply chain analysis.

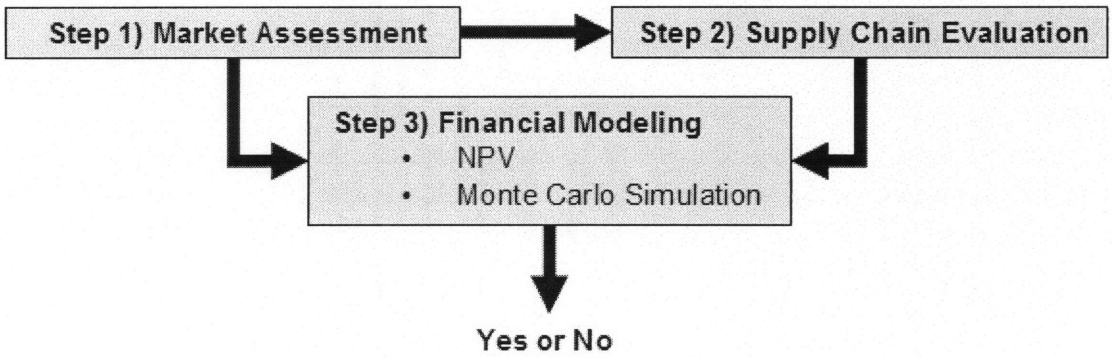


Figure 4-1: A Focus on Financial Modeling

4.1 Net Present Value

Net Present Value (NPV) is a very popular method used across industries in project evaluation. It is based on the principle that money today is worth more than an identical amount received in the future. Therefore, financial evaluation of a project investment should reflect this time value of money.

Figure 4-2 shows the formula for calculating NPV. The cost stream is subtracted from the cash flow to obtain the net stream of revenues, which is then discounted to present value. A project with a positive NPV indicates that future returns exceed investment expectations and, based on financial reasons alone, the project should be accepted. The higher the NPV the more financially valuable is the opportunity.

$$NPV = \sum_{t=1}^{T} \frac{C_t}{(1+r)^t} - C_o$$

Co= Initial Investment
Ct= Cash Flow in year t
r= discount rate
T= time

Figure 4-2: Net Present Value Formula

In order to calculate a project's NPV a company must forecast future cost and revenue streams and identify an appropriate discount rate. The revenue likely to be generated by the project will largely be dependent on the size of commercialization efforts, competition, and structure of the market. A company must also choose an appropriate discount rate. The discount rate usually reflects the return a company expects to earn on an alternative investment with the same risk profile. In this case, the rate of return would have been comparable to other high risk investment.

Advantages & Disadvantages of NPV

The advantage to using an NPV model is that it is simple and consistent. It is reasonable to use this model for project evaluations when there are reliable sources of information and substantial returns. There are however, a number of key disadvantages to the NPV approach. NPV is deterministic and only focuses on the most likely project outcome. It does not account for risks and assumes all revenues and costs are known, assigning single point estimates to variables that have inherent uncertainty.

4.2 Monte Carlo Simulation

Many projects involve elements of uncertainty that are difficult to solve analytically and difficult to assess visually. For example, variables such as growth rate, market size, and market share, which may be elements in calculating expected returns, may each have a range of values associated with them. Usually there are too many combinations of variables to calculate all possible results. Monte Carlo simulation is a sophisticated technique that allows the user to visually capture the range of outcomes associated with the project (*24*).

How Does It Work?

Software packages that utilize Monte Carlo simulation will simply use the spreadsheet model. Each uncertain cell in your spreadsheet can be described with a range of possible values or assigned a specific probability distribution based on historical data. Monte Carlo simulation then generates independent random numbers for each uncertain cell, adhering to each cell's defined probability distribution, and calculates an outcome. It is an iterative process, Figure 4-3, and the simulation continues to run though the model until it reaches a designated maximum trial run. The model then displays all of the results in a continuous distribution of outcomes along with its associated probability, Figure 4-4.

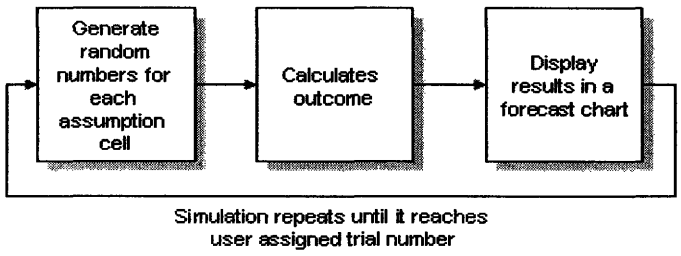
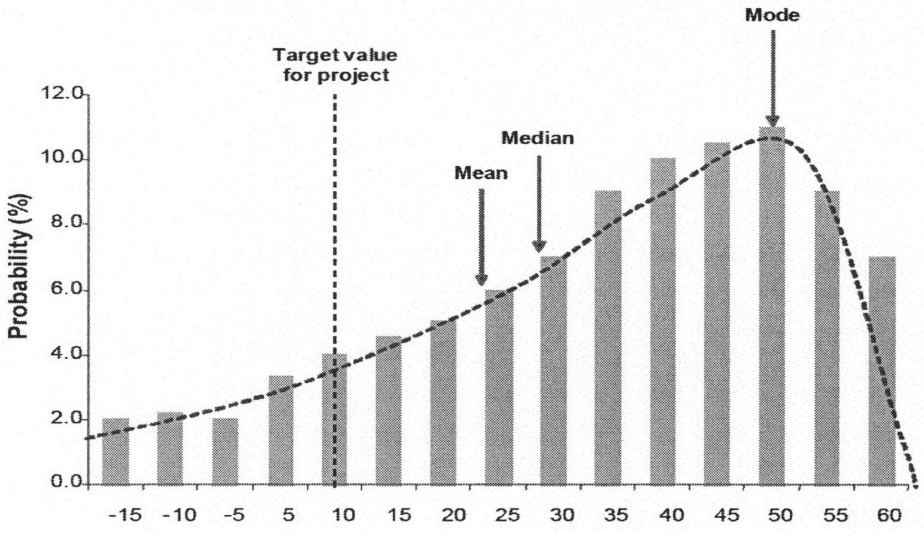


Figure 4-3: Monte Carlo Simulation sample run (22)

The variability in the outcome cell is a function of the variability in the input cells. Users can often conduct sensitivity analysis to determine the impact of each input variable on the distribution of expected outcomes. The simulations also provide the expected means, medians, and modes of project outcomes and details the likelihood a project will meet or exceed its expected result. All this information together is one way to assess project risk.



Source: Effective organization and decision-making for long term growth: Business Insights, Steven Seget

Figure 4-4: Monte Carlo Simulation Outre– Illustration (*21*)

Advantages & Disadvantages of Monte Carlo

The advantage to using Monte Carlo simulation is that it makes risk more explicit and allows the decision maker to see the full range of expected returns of investment. Monte Carlo Simulation also uses NPV principles but the outcome is variable rather than fixed. Because the simulation can undertake thousands of trials, it is fast and useful in evaluating complex projects. Software that utilizes Monte Carlo simulation, usually conducts sensitivity analysis which allows the user to identify key sources of risk and their impact. This in turn means users can more efficiently use their time by focusing on specific variables to reduce the variance in the probability outcomes. The disadvantage to Monte Carlo simulation is that it relies on the probability assumptions made by the user and is more complex to develop and implement than NPV models.

4.3 Financial Modeling of the Cholestagel Project

The value of the Cholestagel introduction can be calculated as a discounted Profit stream (Equation 4-1) or discounted Revenue Stream (Equation 4-2) from 2009 to 2014 (patent expires). These streams are subject to uncertainty in market growth and market share. Mathematically we have:

$$\mathbf{GP} = \sum_{i=4}^{n=9} \frac{r_o (1+X)^i}{(1+\alpha)^i} Y c_i \left[1 - \frac{d a_i t}{p} \right] - \frac{f}{(1+\alpha)^i} \quad \textbf{(Equation 4-1)}$$

$$\mathbf{AR} = \sum_{i=4}^{n=9} \frac{r_o (1+X)^i}{(1+\alpha)^i} Y c_i \quad \textbf{(Equation 4-2)}$$

The symbols are explained in the table below; random variables are in capital letters.

Symbol	Description	Value
GP	Gross Profit	Model output – random variable
AR	Accumulated Revenue	Model output – random variable
X	Growth Rate (estimated)	Random Variable 30%-50% Triangular distribution
Y	Cholestagel Market Share	Random Variable 1-5% Triangular distribution
r_o	Hyperlipidaemia Market (16 cities)	$54 million
p	Wholesale Price (estimated)	Proprietary ($)
α	Discount Rate	10%
c_i	Reimbursement Status constant	½ for i=4, 5 and 1 for i > 5
a_i	Cost of Goods (Raw Material→ Tabletting)	Proprietary ($/MT)
t	Import Tax	4%
d	Daily Dose of Pharmaceutical Ingredient	3.75 g
f	Fixed Costs	Proprietary ($ million)

Assumptions:
Below we list the assumptions taken into consideration during the financial analysis.

- Gross Profit: Does not include costs associated with Marketing and Distribution. These values will need to be decided during negotiation before market entry. The Gross Profit numbers that are output by the model must be large enough to reasonably cover marketing and distribution costs.
- Hyperlipidaemia Growth: The hyperlipidaemia market includes sales of generic, local, and branded pharmaceutical products. The calculations do not distinguish amongst the different forms of products and will assume that the growth rate is the same for the entire market.
- Reimbursement Policy: Since each province has its own reimbursement list, achieving reimbursement status will vary from province to province. However, to simplify the calculation, we assumed that it would only require 2 years to achieve reimbursement status for all 16 cities in their respective provinces.
- Cholestagel Market Share: Market share will be 50% of estimated maximum market share for the two years the drug is not added to the reimbursement list.

- Revenue Projection: The model only runs until the patent life of the drug ends in 2014. In the U.S, generics often enter the market at the end of a branded drug's patent life, significantly affecting the branded drug's market share. However, the concept of patent protection and intellectual property rights is fairly new to China, so it is unclear at this point how much sales will be affected once patent life ends.
- Losses Due to Parallel Trade: It is unlikely that products produced in China will affect WelChol sales in the US. This risk was not added into the financial model
- Fixed Costs: Yearly recurring costs: Administrative Expense at Tabletting Site and Genzyme, Tablet and Printing Tooling, Stability Tests, Release Testing, Maintaining Import License

Up-Front Investments:
Up Front Investment costs are likely to range from roughly $1 to $1.5 million. This can be considered a semi-fixed cost, meaning it only has be paid if they decide to sell Cholestagel in the China Market, but it they do enter this market then this cost is independent of actual volume sold. The main costs include: Registration, Clinical Trials, in-country quality testing site.

Results:
The Gross Profit (GP) and Accumulated Revenue (AR) are functions of the input variables and since these quantities are random, GP and AR can be considered to be random variables themselves. They are difficult to characterize analytically, but can be described with the help of Monte Carlo simulation. I used Crystal Ball add-on to Excel to run my model. For proprietary reasons, only results for Accumulated Revenue is shown below, Fig 4-5.

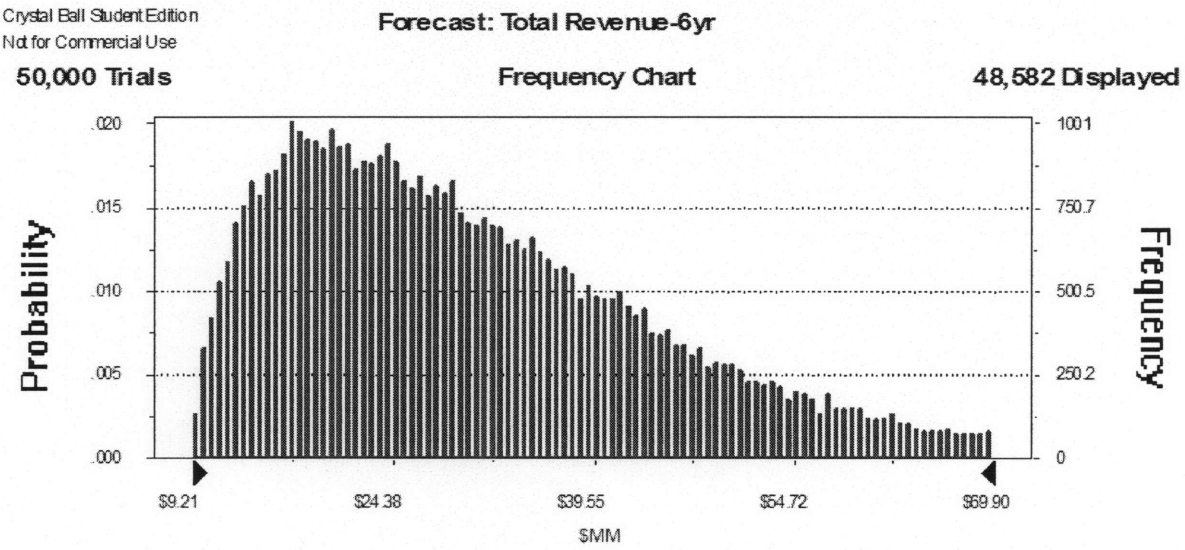


Figure 4-5: Monte Carlo Simulation: Projected Accumulated Revenue for Cholestagel Sales 2009-2014

According to output of the model, the expected accumulated revenue from the venture is $31.6 million. However, there is considerable uncertainty around that number. In fact, the standard

deviation is $15.9 million. There is a 70% probability to have accumulated revenue be between $15.7 million and $47.5 million. The accumulated revenue displays a factor three difference within one standard deviation of the mean and is indicative of the risk and uncertainty associated with this venture.

Figure 4-5 does not account for the costs to produce, market, or distribute Cholestagel. Genzyme has a good estimate on production costs, but does not have great estimates for marketing and distribution in China. From previous discussion in *Section 3.5 Cholestagel Supply Chain Evaluation* we are reminded that drug pricing in China is much lower than in the U.S. As a result production, marketing, and distribution costs will be a large percentage of drug sale price and significantly affect what Genzyme will receive in profits. Based on our experience with WelChol in the U.S., on average Genzyme receives approximately 8% of Gross Revenue. This royalty is pure profit. If we assume the same royalty structure for the China market, we can get a continuous distribution of possible accumulated royalty with its associated probability by multiplying accumulated revenue by 8%. Figure 4-6, shows the output of the Monte-Carlo Model and highlights the accumulated royalty of $1.5 million, the point where Genzyme breaks even on its upfront $1.5 million investment. In Table 4-1, we list the probability to achieve various accumulated royalty streams (column 2) and list the average value in column 3, assuming six years of sales. The table shows a high probability for Genzyme to break-even, 78% probability of reaching $1.5 million. However, there is only a 40% chance Genzyme will make $2.6 million accumulated royalty or $1.1 million in total profits after taking out investment costs.

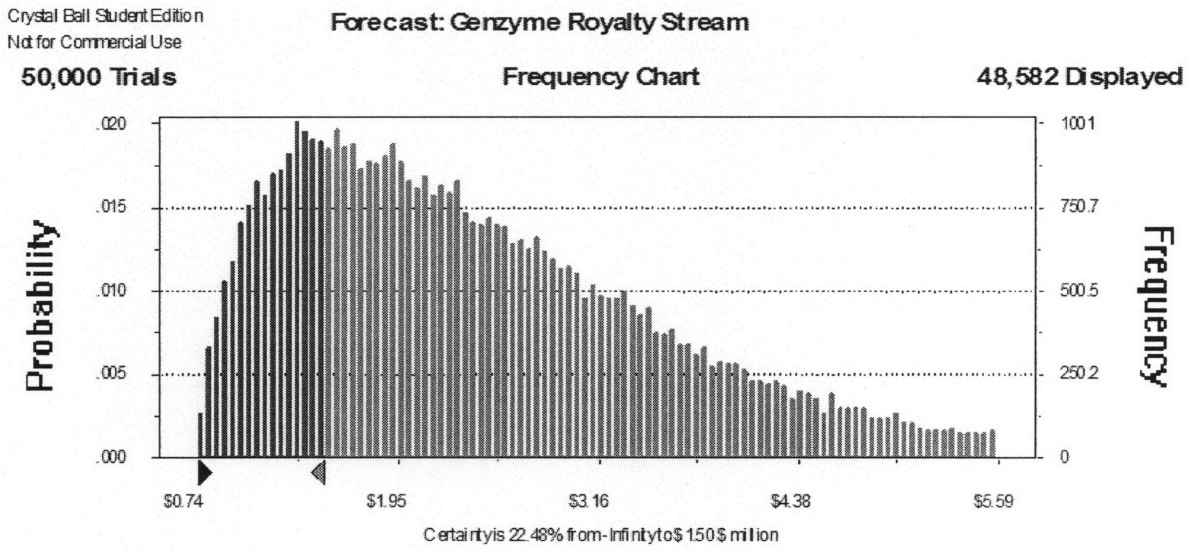


Figure 4-6: Monte Carlo Simulation: Genzyme's Royalty Stream, break-even point

Probability (%)	Accumulated Royalty ($ million)	Per Year Royalty ($ million)
100	0.73	0.12
90	1.17	0.19
80	1.43	0.24
70	1.69	0.28
60	1.96	0.33
50	2.26	0.38
40	2.58	0.43
30	2.97	0.49
20	3.46	0.58
10	4.25	0.71
0	9.90	1.65

Table 4-1: Probability of achieving various Cholestagel royalty streams in China

4.4 Conclusion

In this thesis, I have developed a three-step framework that emphasizes a data-driven approach for analyzing the potential for introducing a pharmaceutical product into a predetermined emerging market. The first step is market assessment which relies on information gathered from primary data (current and prospective customers) and secondary data (third party sources) to better understand the competitive environment. The second step focuses on the supply chain. Information from market research is used to propose and evaluate alternative operational structures, to reduce costs, and to facilitate market entry.

The third-step involves financial modeling of the venture. Because entering an emerging market is characterized by a great deal of uncertainty, I focused on probabilistic Monte Carlo models. This enabled me to make explicit many of the risks and uncertainties inherent in the venture. Rather than having very speculative discussions of possible project outcomes, discussions could be narrowed down to a more structured and fact-based analysis of specific input variables. Modern simulation tools enabled us to see how uncertainties in these assumptions translated into a range of possible project outcomes. This probability distribution of outcomes could then be compared with the company's overall strategic objectives and willingness to take risk, in order to make a sensible final decision.

The framework was used to analyze Genzyme's possible introduction of the cholesterol lowering drug, Cholestagel (WelChol as it is known in the U.S.), into the urban Chinese market. The case study conclusions are outlined below:

The hyperlipidaemia market is China was valued at $92 million in 2005 with impressive growth rates of nearly 30% in the past two years. However, the market is competitive and all of the major anti-hyperlipidaemia brands have already been introduced. Physicians were most interested in Cholestagel as a combination therapy and believed that its non-systemic mode of

action was a key advantage. Even so, physicians were quick to compare Cholestagel to Zetia, a Schering Plough product with similar attributes which is expected to appear on the China Market in mid-2006. Without a strong key differentiator, Cholestagel might be forced to compete on price.

On the cost side, aside from API volume discounts being applied to Cholestagel for the China market, we were unable to find additional cost savings through changes in the supply chain from Raw Material production through Tabletting. Production, marketing, and distribution costs will be a large percentage of drug sale price and significantly affect what Genzyme will receive in profits.

Genzyme collects approximate $10 million per year in royalties from the sale of WelChol in the U.S. Assuming this royalty remains constant until the patent expires in 2014, the net present value of the accumulated WelChol royalty is $63 million, discounted at 10%. The financial Monte Carlo model suggests that the Cholestagel venture in China has a high 78% probability of breaking even, reaching $1.5 million. However, there is only a 40% probability of making an additional $2.6 million in accumulated royalty or $1.1 in total profits by the end of 2014. Cholestagel sales in China would represent 1.7% increase in profits from what Genzyme achieves with WelChol. The expected financial returns do not justify deploying Genzyme resources to manage Cholestagel in this new market environment. Finally, we mention that Genzyme is nevertheless considering taking Cholestagel into the Chinese market for non-economic strategic reasons such as gaining market experience and creating brand awareness.

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5 Appendix A

Sources of International Marketing Data

Market research is critical piece to evaluating whether introducing a product into a new market is advisable. Arguably, the most challenging aspect of evaluating an international market, especially one in a developing country, is obtaining reliable data.

Obtaining reliable information requires persistence, a little creativity, and use of good judgment. Below is a look at the challenges in collecting primary and secondary international marketing data, and ways in which to obtain free or low-cost information (*25*).

Primary vs. Secondary Research

Ideally, business plans should be evaluated based on primary data, data collected specifically for the project plan in question. In comparison to secondary data, which comes from existing third party sources, primary data is more accurate, relevant, and timely. Companies will typically start with secondary sources before turning to costly primary data. For developing markets, collecting primary or secondary data can be extremely challenging.

Obstacles to Collecting Secondary Data in Emerging markets

- *Lack of Current Data*
  In the U.S., we are accustomed to having access to up-to-date data. For example, in the U.S., a Red Book is published each year listing wholesale prices for drugs. Similar books for drugs on the major European markets can easily be found online or with a little searching in libraries. However, in developing countries, similar data is more likely to be collected every 5 to 10 years or not collected at all.

- *Costs of Obtaining Secondary Data*
  When government spending on statistical reporting is low, companies must rely on specialized agency data collection. Because of the challenges in collecting accurate and timely data, these agencies can charge a premium price for the information.

- *Comparability*
  Data collection methods can differ between sources and can lead to conflicting data. Be careful to understand how the numbers are defined.

Obstacles to Collecting International Primary Data

Colleting primary data can have its own difficulties. Below is a list of some of these challenges.

- *Language*
  Communicating with people in a foreign market is more challenging because of the language barrier. Surveys have to be translated, and reverse translated in order to assess if the data collected is consistent with research goals. Even then, there are always moments of miscommunication leading to increased delays in completing the research.

- *Cultural*
  Cultural attitudes can affect how subjects respond towards research surveys. Some societies are uncomfortable with sharing personal information or opinions. Out of politeness, some respondents may choose to agree with opinions in a group setting (focus groups), and are more apt to provide true opinions on a one-to-one interview.

- *Infrastructure*
  Local infrastructure may affect data collection techniques applied for the market research. In the U.S., there are sophisticated telephone software and internet survey methods, which can provide affordable and accurate surveys. In foreign markets, where there are infrastructure constraints, primary data rely on face-to-face interviews, which are more prone to error. In addition, this survey method limits the size of the interview pool due to time constraints.

Recommendations for Resolving International Data Challenges
There are a number of resources, free or low-cost, which can help mitigate some of the data challenges faced during market research.

Public Resources
- Scientific Journals: This researcher found epidemiology reports to be an excellent source of statistical information. The studies are specific to a disease group and can provide prevalence information which can be used in market sizing.

- Industry Press: Newspapers and industry magazines like The Wall Street Journal, New York Times, and the Harvard Business Review will often detail competing company activities. Company literature and websites are also good sources of competitive intelligence.

- Databases: There are government databases with statistical information such as population, GDP, and per capita income. These websites include STAT-USA (www.stat-usa.gov), CIA World Factbook (www.cia.gov/cia/publications/factbook), and National Bureau of Statistics of China www.stats.gov.cn/enGliSH/)

- Specialized Research Reports: Most detailed research reports must be purchased from specialized companies but occasionally detailed reports can be found through the university library resources, or outdated/stripped down versions might be posted on-line.

Networking
- Personal Resource: This researcher was able to speak to someone who had worked in the Chinese healthcare industry, and to a regular purchaser of cholesterol lowering drugs in China.

- Company Resource: It may be fruitful to speak with employees within other business units, who may have experience in either entering new markets or in entering the market of interest. These individuals may already have the information you are seeking or have access to relevant resources.

6 Appendix B

Market Research Study

Genzyme hired a marketing firm to conduct primary research to better understand the anti-hyperlipidaemia market in China. The research included focus groups and face-to-face interviews with physicians at top tier hospitals in 6 major urban cities. The study was started in October 2005 and was completed at the end of December 2005. The information gathered focused on the following key deliverables:

- To explore the potential of Cholestagel in the anti-hyperlipidaemia market in China
  - An analysis of the market with regard to geography (city tiers) and IMS data analysis
  - Reimbursed sales vs. out-of-pocket purchasers
  - Points of distribution (hospital or retail pharmacy channels)
  - Age analysis of patients
  - Pipeline products scheduled to enter the market
  - Pricing structure of all existing therapies
- To identify potential market positions for Cholestagel, both currently and in the future.

Focus Group Interviews

- Chief Doctor (CD) or Vice-Chief Doctor (VCD) level physicians were recruited from Tier III hospitals (highest level)
- Two focus groups were conducted, each lasting 90-120 minutes, one in Shanghai and one in Beijing.

Beijing Hospitals: 7 physicians	**Department & Seniority**
Tongren Hospital	Cardiology (VCD)
Ji shui tan Hospital	Cardiology (CD)
Ren ming Hospital	Cardiology (VCD)
Beijing Hospital	Cardiology (CD)
Chao yang Hospital	Geriatrics (VCD)
Zhong ri Hospital	Geriatrics (VCD)
You yi Hospital	Cardiology (VCD)
Shanghai Hospitals: 6 physicians	
Huashan Hospital	Geriatrics (CD)
Shanghai NO.1 Hospital	Geriatrics (VCD)
Rui jin Hospital	Cardiology (VCD)
Shanghai NO.9 Hospital	Cardiology (VCD)
Shuguang Hospital	Cardiology (CD)
Navy NO. 411 Hospital	Cardiology (CD)

Face-to-Face Interviews

- Interviews lasted around 30 minutes each. The questionnaire followed a semi-structured format, including both open and closed questions.
- A total of 160 doctors were interviewed.
- At the end of the interview the doctors were asked to fill in at least 10 hyperlipidaemia patient diary forms. Each form covered the demographics, diagnosis and treatment of patients receiving therapy for their hyperlipidaemia.

		Count	Col %
City Level	Tier 1 cities	100	63%
	Tier 2 cities	60	38%
	Total	160	100%
City	Beijing (BJ)	35	22%
	Shanghai (SH)	35	22%
	Guangzhou (GZ)	30	19%
	Wuhan (WH)	20	13%
	Shenyang (SY)	20	13%
	Chengdu (CD)	20	13%
	Total	160	100%
Hospital Level	Tier III hospital	103	64%
	Tier II hospital	57	36%
	Total	160	100%
Seniority	(Vice) Chief Doctor (CD/VCD)	96	60%
	Doctor in Charge (DIC)	64	40%
	Total	160	100%
Department	Cardiology (Card.)	115	72%
	Geriatrics (Ger.)	45	28%
	Total	160	100%

China Visit

Top managers in the pharmaceutical division at Genzyme, the business unit that manages Cholestagel, including this researcher, visited China to meet with five potential marketing and distribution partners. The one week trip began November 27, 2005 and included visits to Beijing and Shanghai.

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